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BOX: PATENT APPLICATION

SIR:

Transmitted herewith for filing is the patent application (including Specification, Claims, and Abstract, 27 pages) of:

Inventors : **Dennis Gonsalves and Kai-Shu Ling**For : **GRAPEVINE LEAFROLL VIRUS PROTEINS AND THEIR USES**

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**TITLE: GRAPEVINE LEAFROLL VIRUS PROTEINS AND
THEIR USES**

INVENTOR: Dennis Gonsalves and Kai-Shu Ling

DOCKET NO.: 19603/2842 (CRF D-1676D)

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GRAPEVINE LEAFROLL VIRUS PROTEINS AND THEIR USES

Cross-reference to Related Applications

This application claims the benefit of U.S. Provisional Patent Application
5 Serial No. 60/083,404, filed April 29, 1998.

Statement as to Federally Sponsored Research

This work was supported by U.S.-Israel Binational Agricultural Research and
Development Fund Grant No. US-1737-89 and by the U.S. Department of Agriculture
10 Cooperative Agreement No. 58-2349-9-01. The Federal Government may have
certain rights in the invention.

Background of the Invention

The present invention relates to grapevine leafroll virus genomic DNA, RNA,
15 proteins encoded thereby, and their uses.

The world's most widely grown fruit crop, the grape (*Vitis sp.*), is cultivated on
all continents except Antarctica. Many plant pathogens, such as fungi, bacteria,
phytoplasmas, viruses, and nematodes can infect grapes, and the resultant diseases can
cause substantial losses in production thereof (Pearson et al., Compendium of Grape
20 Diseases, American Phytopathological Society Press (1988)). Among these, viral
diseases constitute a major hindrance to profitability.

About 34 viruses have been isolated and characterized from grapevines. The
major virus diseases are grouped into: (1) nepoviruses, (2) the leafroll complex
(GVLR), and (3) the rugose wood complex (Martelli, ed., Graft Transmissible
25 Diseases of Grapevines, Handbook for Detection and Diagnosis, FAO, UN, Rome,
Italy (1993)). The grapevine leafroll complex (GVLR) is most widely distributed
throughout the world. The virus was first identified in 1946 by Harmon et al. (Proc.
Am. Soc. Hort. Sci. 74:190-194 (1946)) and later confirmed by Goheen et al.
(Phytopathology, 48:51-54 (1958)). Leafroll is a serious virus disease and occurs
30 wherever grapes are grown. Although the disease is not lethal, it causes yield losses
and reduction in sugar content. For example, the amount of sugar in individual berries

of infected vines is only about 1/2 to 2/3 that of berries from noninfected vines (Goheen, supra).

Several virus particle types have been isolated from leafroll diseased vines. These include potyvirus-like (Tanne et al., *Phytopathology*, 67:442-447 (1977)), isometric virus-like (Castellano et al., *Vitis*, 22:23-39 (1983)) and closterovirus-like (Namba, *Ann. Phytopathol. Soc. Japan*, 45:497-502 (1979)) particles. In recent years, however, long flexuous closteroviruses ranging from 1,400 to 2,200 nm have been most consistently associated with leafroll disease as shown, for example, in Castellano (1983), Faoro et al., *Riv. Patol. Veg., Ser IV*, 17:183-189 (1981), Hu et al., *J. Phytopathol.*, 128:1-14 (1990), Milne et al., *Phytopathol. Z.*, 110:360-368 (1984), and Zimmermann et al., *J. Phytopathol.*, 130:205-218 (1990). These closteroviruses are referred to as grapevine leafroll associated viruses ("GLRaV"). At least six serologically distinct types of GLRaV's (GLRaV-1 to -6) have been detected from leafroll diseased vines (Boscia et al., *Vitis*, 34:171-175 (1995)).

Grapevine leafroll is transmitted primarily by contaminated scions and rootstocks. Under field conditions, however, several species of mealybugs have been shown to be the vector of leafroll (Engelbrecht et al., *Phytophylactica*, 22:341-346 (1990), Rosciglione, et al., *Phytoparasitica*, 17:63-63 (1989), and Tanne, *Phytoparasitica*, 16:288 (1988)). Specifically, it has been shown that mealybugs transmit grapevine leafroll virus type-3 only and no others. Natural spread of leafroll by insect vectors is rapid in various parts of the world. Prevalence of leafroll worldwide may increase as chemical control of mealybugs becomes more difficult due to the unavailability of effective insecticides.

In view of the serious risk grapevine leafroll virus poses to vineyards and the absence of an effective treatment of it, the need to prevent this affliction continues to exist. The present invention is directed to overcoming this affliction using biotechnology tools and methods to established disease-free grape plants.

Summary of the Invention

In a first aspect, the invention features an isolated grapevine leafroll virus protein or polypeptide selected from the group consisting of: a polyprotein comprising

a proteinase or a methyltransferase; a proteinase; a methyltransferase; a helicase having an amino terminal amino acid sequence consisting of ValGlyGluSer; and a protein consisting of the amino acid sequence of SEQ ID NO: 13.

One preferred protein or polypeptide is a polyprotein having a molecular weight of from 242 to 248 kDa or the polyprotein includes the amino acid sequence of SEQ ID NO: 15.

Another preferred protein is a proteinase that includes the amino acid sequence of SEQ ID NO: 5. Another preferred protein is a methyltransferase that includes the amino acid sequence of SEQ ID NO: 7.

In a second aspect, the invention features an isolated RNA molecule encoding a protein or polypeptide of the first aspect.

In a third aspect, the invention features an isolated DNA molecule that includes the nucleotide sequence of SEQ ID NO: 2.

In a fourth aspect, the invention features an isolated DNA molecule encoding a protein or polypeptide of the first aspect.

In preferred embodiments of the fourth aspect, the protein or polypeptide is a polyprotein having a molecular weight of from 242 to 248 kDa. Preferably, the polyprotein (i) includes the amino acid sequence of SEQ ID NO: 15; (ii) is a proteinase that includes the amino acid sequence of SEQ ID NO: 5; (iii) is a methyltransferase that includes the amino acid sequence of SEQ ID NO: 7; or (iv) is a helicase that includes the amino acid sequence of SEQ ID NO: 9.

In other preferred embodiments of the fourth aspect, the DNA molecule includes the nucleotide sequence of SEQ ID NO: 3, the nucleotide sequence of SEQ ID NO: 4, the nucleotide sequence of SEQ ID NO: 6, or the nucleotide sequence of SEQ ID NO: 8.

In a fifth aspect, the invention features an expression system that includes an expression vector into which is inserted a heterologous DNA molecule of the third or fourth aspect. The heterologous DNA molecule can be inserted in sense orientation or in antisense orientation.

In a sixth aspect, the invention features a host cell transformed with a heterologous DNA molecule of the third or fourth aspect. The host cell can be

selected from the group consisting of *Agrobacterium vitis* and *Agrobacterium tumefaciens*, a grape cell, or a citrus cell.

The DNA molecules of the invention can be used to make transgenic plants or transgenic plant components (e.g., a scion, a rootstock, or a somatic embryo).

5 The invention features also a method for conferring viral disease resistance on a plant or plant component, by: (a) transforming a plant cell with a DNA molecule according to the third or fourth aspect, which is expressed on the plant or plant component; and (b) regenerating a transgenic plant or transgenic plant component from the plant cell. In preferred embodiments, the plant or plant component is
10 resistant to a grapevine leafroll virus selected from the group consisting of GLRaV-1, GLRaV-2, GLRaV-3, GLRaV-4, GLRaV-5, and GLRaV-6. In a related embodiment, the plant or plant component is resistant to a beet yellows virus, lettuce infectious virus, or citrus tristeza.

 In another aspect, the invention features an antibody or binding portion thereof
15 or probe recognizing the protein or polypeptide according to the first aspect.

 In a tenth aspect, the invention features a method for detecting a virus in a sample, the method including: (a) contacting a sample with the antibody of claim 31 under conditions that allow for complex formation between the antibody and the virus; and
20 (b) detecting the complexes as an indication that the virus is present in the sample.

 In an eleventh aspect, the invention features a method for detecting a viral nucleic acid molecule in a sample, the method including: (a) contacting a sample with the DNA of the third aspect or a fragment thereof under conditions that allow for complex formation between the DNA and the virus; and (b) detecting the complexes
25 as an indication that the virus is present in the sample.

 In a twelfth aspect, the invention features a method for detecting a viral nucleic acid molecule in a sample, the method including: (a) contacting a sample with the DNA of the fourth aspect or a fragment thereof under conditions that allow for complex formation between the DNA and the virus; and (b) detecting the complexes
30 as an indication that the virus is present in the sample.

By "plant cell" is meant any self-propagating cell bounded by a semi-permeable membrane and containing a plastid. A plant cell, as used herein, is obtained from, without limitation, seeds, suspension cultures, embryos, meristematic regions, callus tissue, protoplasts, leaves, roots, shoots, somatic and zygotic embryos, as well as any part of a reproductive or vegetative tissue or organ.

By "plant component" is meant a part, segment, or organ obtained from an intact plant or plant cell. Exemplary plant components include, without limitation, somatic embryos, leaves, fruits, scions and rootstocks.

By "transgenic" is meant any cell which includes a nucleic acid molecule (for example, a DNA sequence) which is inserted by artifice into a cell and becomes part of the genome of the organism (in either an integrated or extrachromosomal fashion for example, a viral expression construct which includes a subgenomic promoter) which develops from that cell. As used herein, the transgenic organisms are generally transgenic grapevines or grapevine components and the nucleic acid molecule (for example, a transgene) is inserted by artifice into the nuclear or plastidic compartments of the plant cell.

By "transgene" is meant any piece of a nucleic acid molecule (for example, DNA) which is inserted by artifice into a cell, and becomes part of the organism (integrated into the genome or maintained extrachromosomally) which develops from that cell. Such a transgene may include a gene which is partly or entirely heterologous (i.e., foreign) to the transgenic organism, or may represent a gene homologous to an endogenous gene of the organism.

Grapevine leafroll virus resistant transgenic variants of the current commercial grape cultivars and rootstocks allows for more control of the virus while retaining the varietal characteristics of specific cultivars. Furthermore, these variants permit control of GLRaV transmitted either by contaminated scions or rootstocks or other means. In this manner, as well as others, the interests of the environment and the economics of grape cultivation and wine making are all benefited by the present invention.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Brief Description of the Drawings

Figure 1 shows the genome organization of GLRaV-3 in comparison with the genome organization of GLRaV-2, another closterovirus associated with leafroll
5 disease.

Figure 2 shows the nucleic acid sequence of the GLRaV-3 genomic sequence (SEQ ID NO: 1).

Figure 3 shows the nucleic acid sequence of the 5' untranslated region of GLRaV-3 (SEQ ID NO: 2).

10 Figure 4 shows the nucleic acid sequence of the ORF 1a (SEQ ID NO: 3).

Figure 5 shows the nucleic acid sequence of the proteinase encoded by ORF 1a (SEQ ID NO: 4).

Figure 6 shows the amino acid sequence of the proteinase encoded by the DNA sequence of ORF 1a (SEQ ID NO: 5).

15 Figure 7 shows the nucleic acid sequence of the methyltransferase encoded by ORF 1a (SEQ ID NO: 6).

Figure 8 shows the amino acid sequence of the methyltransferase encoded by ORF 1a (SEQ ID NO: 7).

20 Figure 9 shows the amino acid alignment of various closterovirus methyltransferases.

Figure 10 shows the nucleic acid sequence of the helicase encoded by ORF 1a (SEQ ID NO: 8).

Figure 11 shows the amino acid sequence of the helicase encoded by ORF 1a (SEQ ID NO: 9).

25 Figure 12 shows the nucleic acid sequence of ORF 1b (SEQ ID NO: 10).

Figure 13 shows the amino acid sequence of the polypeptide encoded by ORF 1b (SEQ ID NO: 11).

Figure 14 shows the nucleic acid sequence of ORF 11 of the present invention (SEQ ID NO: 12).

30 Figure 15 shows the amino acid sequence of the protein encoded by ORF 11 of the present invention (SEQ ID NO: 13).

Figure 16 shows the amino acid sequence listing of the protein encoded by ORF 1a (SEQ ID NO: 15).

Figure 17 shows the nucleic acid sequence of the 3' untranslated region of GLRaV-3 (SEQ ID NO: 14).

5

Detailed Description of the Invention

The present invention relates to isolated DNA molecules encoding proteins or polypeptides of grapevine leafroll virus (type 3) ("GLRaV-3") as well as the 5' untranslated and 3' untranslated regions associated therewith. Applicants have
10 completely sequenced the entire GLRaV-3 genome, which contains 13 open reading frames ("ORFs") as compared to the genome of GLRaV-2 (Figure 1). The DNA molecule for the entire GLRaV-3 genome has a nucleotide sequence corresponding to SEQ ID NO: 1 as given in Figure 2.

A 5' untranslated region ("UTR") extends from nucleotides 1-158 of SEQ ID
15 NO: 1 and is listed separately as SEQ ID NO: 2, as shown in Figure 3. The first ORF appearing near the 5' end of the complete GLRaV-3 genome is ORF 1a. The DNA molecule encoding ORF 1a extends from nucleotides 159-6872 of SEQ ID NO: 1 and has a nucleic acid sequence corresponding to SEQ ID NO: 3, as shown in Figure 4. This sequence encodes for a large, GLRaV-3 polyprotein having a molecular weight
20 of about 242-248 kDa, more preferably 245.2 kDa. It is believed this DNA molecule encodes a large, GLRaV-3 polyprotein containing the conserved domains of a proteinase, a methyltransferase, and a helicase.

The proteinase domain found in ORF 1a is encoded by nucleotides 411-770 of SEQ ID NO: 1 and has a nucleic acid sequence comprising SEQ ID NO: 4, as shown
25 in Figure 5. The proteinase domain has an amino acid sequence comprising SEQ ID NO: 5, as given in Figure 6, and is similar to that described for Hepatitis C virus (Hijikata et al., Proc. Natl. Acad. Sci. USA 90:10773-10777 (1993), which is hereby incorporated by reference).

The methyltransferase domain found in ORF 1a is encoded by nucleotides
30 1536-2351 of SEQ ID NO: 1 and as has a nucleic acid sequence comprising SEQ ID NO: 6, as shown in Figure 7. The methyltransferase domain has an amino acid

sequence comprising SEQ ID NO: 7, as shown in Figure 8. As shown in Figure 9, the methyltransferase domain is similar to methyltransferase domains of other closteroviruses.

The helicase domain found in ORF 1a is encoded by nucleotides 5922-6794 of
5 SEQ ID NO: 1 and has a nucleic acid sequence comprising SEQ ID NO: 8, as shown in Figure 10. The helicase domain has an amino acid sequence comprising SEQ ID NO: 9, as shown in Figure 11.

Another open reading frame of the present invention is found within the GLRaV-3 genome and is designated ORF 1b. This open reading frame is believed to
10 encode a RNA-dependent RNA-polymerase ("RdRp"). The DNA molecule encoding ORF 1b extends from nucleotides 6877-8475 of SEQ ID NO: 1 and has a nucleic acid sequence corresponding to SEQ ID NO: 10, as shown in Figure 12.

The RdRp encoded by the DNA molecule of SEQ ID NO: 10 has an amino acid sequence corresponding to SEQ ID NO: 11, as shown in Figure 13. The protein
15 has a molecular weight of about 58 kDa to 64 kDa, with 61 kDa being most preferred.

Additional ORFs found in GLRaV-3 genome (SEQ ID NO: 1) are as follows: ORF 2 comprises nucleotides 8708-8863; ORF 3 comprises nucleotides 9930-10067; ORF 4 comprises nucleotides 10086-11735; ORF 5 comprises nucleotides 11728-13179; ORF 6 comprises nucleotides 13269-14210; ORF 7 comprises
20 nucleotides 14273-15706; ORF 8 comprises nucleotides 15717-16274; ORF 9 comprises nucleotides 16271-16804; and ORF 10 comprises nucleotides 16811-17350.

ORF 11, which is found in the GLRaV-3 genome (SEQ ID NO: 1) at nucleotides 17353-17463, is given herein as SEQ ID NO: 12 and shown in Figure 14.
25 The ORF encodes a protein having about 36 amino acids (SEQ ID NO:13), which is shown in Figure 15.

ORF 12 is found in the GLRaV-3 genome (SEQ ID NO: 1) at nucleotides 17460-17642. Afterwards, a 3' untranslated regions is observed at nucleotides 17643-17919 of SEQ ID NO: 1.

30 Also encompassed by the present invention are fragments of the DNA molecules of the present invention. Suitable fragments capable of imparting viral

resistance to plants and plant components are constructed by using appropriate restriction sites, revealed by inspection of the DNA molecule's sequence, to: (i) insert an interposon (Felley et al., Gene, 52:147-15 (1987)) such that truncated forms of the GLRaV-3 polypeptide or protein, lacking various amounts of the C-terminus, can be produced or (ii) delete various internal portions of the protein. Alternatively, the sequence can be used to amplify any portion of the coding region, such that it can be cloned into a vector supplying both transcription and translation start signals. In addition, the 5' untranslated region, or any other portion of the genome, can also be used and expressed either in a sense or antisense to effect viral control within the plant.

Variants may also (or alternatively) be modified by, for example, the deletion or addition of nucleotides that have minimal influence on the properties, secondary structure and hydropathic nature of the encoded polypeptide. For example, the nucleotides encoding a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein that co-translationally or post-translationally directs transfer of the protein to a particular site or organelle. The nucleotide sequence may also be altered so that the encoded polypeptide is conjugated to a linker or other sequence for ease of synthesis, purification, or identification thereof.

The grapevine leafroll virus proteins or polypeptides of the invention are preferably produced in purified form (preferably, at least about 80%, more preferably 90%, pure) by conventional techniques. For example, the protein or polypeptide of the invention is isolated by lysing and sonication. After washing, the pellet is resuspended in buffer containing a suitable buffer such as Tris-HCl. During dialysis, a precipitate forms from this protein solution. The solution is centrifuged, and the pellet is washed and resuspended in the buffer containing said suitable buffer. Proteins are resolved by electrophoresis through a SDS 12% polyacrylamide gel.

Any of the DNA molecules described herein can be incorporated in cells using conventional recombinant DNA technology. It is not necessary for the DNA molecules to be expressed in a manner that results in protein production in order to be within the scope of the present invention. For example, the introduced DNA molecule may express 158 nucleotides of 5' untranslated region. Furthermore, the skilled

artisan may take any of the DNA sequences included herein and may place these sequences in a manner to result in antisense expression, frame shift mutations, or any other manner available to the skilled artisan that results in mRNA production without facilitating translation.

5 Generally, a DNA molecule to be expressed involves inserting said molecule into an expression system to which the DNA molecule is heterologous (i.e., not normally present). The heterologous DNA molecule is inserted into the expression system or vector in proper sense orientation and correct reading frame. As stated previously, it may also be desired to place the DNA molecule in a orientation that
10 results in a incorrect reading frame. Regardless of reading frame preference, the vector contains the necessary elements for the transcription and translation of the inserted protein-coding sequences.

 U.S. Patent No. 4,237,224 to Cohen and Boyer, hereby incorporated by reference, describes the production of expression systems in the form of recombinant
15 plasmids using restriction enzyme cleavage and ligation with DNA ligase. These recombinant plasmids are then introduced by means of transformation and replicated in unicellular cultures including prokaryotic organisms and eukaryotic cells grown in tissue culture.

 Recombinant genes may also be introduced into viruses, such as vaccinia
20 virus. Recombinant viruses can be generated by transfection of plasmids into cells infected with virus.

 Suitable vectors include, but are not limited to, the following viral vectors such as lambda vector system gt11, gt WES.tB, Charon 4, and plasmid vectors such as pBR322, pBR325, pACYC177, pACYC184, pUC8, pUC9, pUC18, pUC19, pLG339,
25 pR290, pKC37, pKC101, SV 40, pBluescript II SK +/- or KS +/- (see "Stratagene Cloning Systems" Catalog (1993) from Stratagene, La Jolla, CA, hereby incorporated by reference), pQE, pIH821, pGEX, pET series (see Studier et. al., Gene Expression Technology, vol. 185 (1990), hereby incorporated by reference), and any derivatives thereof.

30 Recombinant molecules can be introduced into cells via transformation, transduction, conjugation, mobilization, electroporation, and the like. The DNA

sequences are cloned into the vector using standard cloning procedures in the art, as described by Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Springs Laboratory, Cold Springs Harbor, New York (1982), hereby incorporated by reference.

5 A variety of host-vector systems may be utilized to express the protein-encoding sequence(s). Primarily, the vector system must be compatible with the host cell used. Host-vector systems include but are not limited to the following: bacteria transformed with bacteriophage DNA, plasmid DNA, or cosmid DNA; microorganisms such as yeast containing yeast vectors; mammalian cell systems
10 infected with virus (e.g., vaccinia virus, adenovirus, etc.); insect cell systems infected with virus (e.g., baculovirus); and plant cells infected by bacteria or transformed via particle bombardment (i.e. biolistics). The expression elements of these vectors vary in their strength and specificities. Depending upon the host-vector system utilized, any one of a number of suitable transcription and translation elements can be used.

15 Different genetic signals and processing events control many levels of gene expression (e.g., DNA transcription and messenger RNA ("mRNA") translation). Transcription of DNA is dependent upon the presence of a promoter which is a DNA sequence that directs the binding of RNA polymerase and thereby promotes mRNA synthesis. The DNA sequences of eukaryotic promoters differ from those of
20 prokaryotic promoters. Furthermore, eukaryotic promoters and accompanying genetic signals may not be recognized in or may not function in a prokaryotic system, and, further, prokaryotic promoters may not be recognized and may not function in eukaryotic cells.

 Similarly, translation of mRNA in prokaryotes depends upon the presence of
25 the proper prokaryotic signals which may differ from those of eukaryotes. Efficient translation of mRNA in prokaryotes may require a ribosome binding site called the Shine-Dalgarno ("SD") sequence on the mRNA. For a review on maximizing gene expression, see Roberts and Lauer, *Methods in Enzymology*, 68:473 (1979), hereby incorporated by reference.

30 Promoters vary in their "strength" (i.e. their ability to promote transcription). For the purposes of expressing a cloned gene, it may be desirable to use strong

promoters in order to obtain a high level of transcription and, hence, expression of the gene. It may also be advantageous, however, to use weak promoters and/or to select plants expressing the transgene at low levels. Depending upon the host cell system utilized, any one of a number of suitable promoters may be used. For instance, when
5 cloning in *E. coli*, its bacteriophages, or plasmids, promoters such as the T7 phage promoter, *lac* promoter, *trp* promoter, *recA* promoter, ribosomal RNA promoter, the P_R and P_L promoters of coliphage lambda and others, including but not limited, to *lacUV5*, *ompF*, *bla*, *lpp*, and the like, may be used to direct high levels of transcription of adjacent DNA segments. Additionally, a hybrid *trp-lacUV5* (*tac*)
10 promoter or other *E. coli* promoters produced by recombinant DNA or other synthetic DNA techniques may be used to provide for transcription of the inserted gene.

Bacterial host cell strains and expression vectors may be chosen which inhibit the action of the promoter unless specifically induced. In certain operons, the addition of specific inducers may be necessary for efficient transcription of the inserted DNA.
15 For example, the *lac* operon is induced by the addition of lactose or IPTG (isopropylthio-beta-D-galactoside). A variety of other operons, such as *trp*, *pro*, etc., are under different controls.

Specific initiation signals may also be required for efficient gene transcription and translation in prokaryotic cells. These transcription and translation initiation
20 signals may vary in "strength" as measured by the quantity of gene specific messenger RNA and protein synthesized, respectively. The DNA expression vector, which contains a promoter, may also contain any combination of various transcription and/or translation initiation signals. All of these techniques are well known to the artisan skilled in the art of molecular biology.

25 Once the isolated DNA molecules derived from GLRaV-3, as described above, have been cloned into an expression system, they are ready to be incorporated into a host cell. Such incorporation can be carried out by the various forms of transformation noted above, depending upon the vector/host cell system. Suitable host cells include, but are not limited to, bacteria, virus, yeast, mammalian cells,
30 insect, plant, and the like.

The present invention also relates to RNA molecules which encode the various GLRaV-3 proteins or polypeptides described above. The transcripts can be synthesized using the host cells of the present invention by any of the conventional techniques. The mRNA can be translated either *in vitro* or *in vivo*. Cell-free systems typically include wheat-germ or reticulocyte extracts. *In vivo* translation can be effected, for example, by microinjection into frog oocytes.

One aspect of the present invention involves using one or more of the above DNA molecules encoding the various proteins or polypeptides of GLRaV-3 to transform plants in order to impart viral resistance to the plants. Most preferred are those DNA molecules as described in SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, and SEQ ID NO: 12. In some cases, the DNA molecules listed herein can also be translated into protein. Those protein sequences most preferred include those listed herein as SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, and SEQ ID: 15. An additional aspect is the use of either the 5' untranslated region (SEQ ID NO: 2) or the 3' untranslated region (SEQ ID NO: 14) to impart viral resistance in plants. The mechanism by which resistance is imparted is not known. In one hypothetical mechanism, the transformed plant can express, e.g., the GLRaV-3 helicase or polypeptide thereof, and, when the transformed plant is inoculated by a grapevine leafroll virus, such as GLRaV1, GLRaV2, GLRaV3, GLRaV4, GLRaV5, or GLRaV6, or combinations of these, or beet yellows virus, lettuce infectious virus, or citrus tristeza, the expressed GLRaV-3 helicase or polypeptide disrupts pathogenesis of the virus.

In this aspect of the present invention the subject DNA molecule incorporated in the plant can be constitutively expressed. Alternatively, expression can be regulated by a promoter which is activated by the presence of grapevine leafroll virus. Suitable promoters for these purposes include those from genes expressed in response to grapevine leafroll virus infiltration.

Any of the isolated DNA molecules described herein can be utilized to impart grapevine leafroll resistance for a wide variety of grapevine plants. Methods for evaluating the resistance of a plant to viral disease are well known in the art. For

example, the level of resistance to viral disease may be determined by comparing physical features and characteristics.

The DNA molecules are particularly well suited to imparting resistance to *Vitis* scion or rootstock cultivars. Scion cultivars which can be protected include

5 those commonly referred to as Table on Raisin Grapes, such as Alden, Almeria, Anab-E-Shahi, Autumn Black, Beauty Seedless, Black Corinth, Black Damascus, Black Malvoisie, Black Prince, Blackrose, Bronx Seedless, Burgrave, Calmeria, Campbell Early, Canner, Cardinal, Catawba, Christmas, Concord, Dattier, Delight, Diamond, Dizmar, Duchess, Early Muscat, Emerald Seedless, Emperor, Exotic,

10 Ferdinand de Lesseps, Fiesta, Flame seedless, Flame Tokay, Gasconade, Gold, Himrod, Hunisa, Hussiene, Isabella, Italia, July Muscat, Khandahar, Katta, Kourgane, Kishmishi, Loose Perlette, Malaga, Monukka, Muscat of Alexandria, Muscat Flame, Muscat Hamburg, New York Muscat, Niabell, Niagara, Olivette blanche, Ontario, Pierce, Queen, Red Malaga, Ribier, Rish Baba, Romulus, Ruby Seedless, Schuyler,

15 Seneca, Suavis (IP 365), Thompson seedless, and Thomuscat. They also include those used in wine production, such as Aleatico, Alicante Bouschet, Aligote, Alvarelhao, Aramon, Baco blanc (22A), Burger, Cabernet franc, Cabernet, Sauvignon, Calzin, Carignane, Charbono, Chardonnay, Chasselas dore, Chenin blanc, Clairette blanche, Early Burgundy, Emerald Riesling, Feher Szagos, Fernao Pires, Flora,

20 French Colombard, Fresia, Furmint, Gamay, Gewurztraminer, Grand noir, Gray Riesling, Green Hungarian, Green Veltliner, Grenache, Grillo, Helena, Inzolia, Lagrein, Lambrusco de Salamino, Malbec, Malvasia bianca, Mataro, Melon, Merlot, Meunier, Mission, Montua de Pilas, Muscadelle du Bordelais, Muscat blanc, Muscat Ottonel, Muscat Saint-Vallier, Nebbiolo, Nebbiolo fino, Nebbiolo Lampia, Orange

25 Muscat, Palomino, Pedro Ximenes, Petit Bouschet, Petite Sirah, Peverella, Pinot noir, Pinot Saint-George, Primitivo di Gioia, Red Veltliner, Refosco, Rkatsiteli, Royalty, Rubired, Ruby Cabernet, Saint-Emilion, Saint Macaire, Salvador, Sangiovese, Sauvignon blanc, Sauvignon gris, Sauvignon vert, Scarlet, Seibel 5279, Seibel 9110, Seibel 13053, Semillon, Servant, Shiraz, Souzao, Sultana Crimson, Sylvaner, Tannat,

30 Teroldico, Tinta Madeira, Tinto cao, Touriga, Traminer, Trebbiano Toscano, Trousseau, Valdepenas, Viognier, Walschriesling, White Riesling, and Zinfandel.

Rootstock cultivars which can be protected include Couderc 1202, Couderc 1613, Couderc 1616, Couderc 3309, Dog Ridge, Foex 33 EM, Freedom, Ganzin 1 (A x R #1), Harmony, Kober 5BB, LN33, Millardet & de Grasset 41B, Millardet & de Grasset 420A, Millardet & de Grasset 101-14, Oppenheim 4 (SO4), Paulsen 775, Paulsen 1045, Paulsen 1103, Richter 99, Richter 110, Riparia Gloire, Ruggeri 225, Saint-George, Salt Creek, Teleki 5A, *Vitis rupestris Constantia*, *Vitis californica*, and *Vitis girdiana*.

There exists an extensive similarity in both the methyltransferase and helicase sequence regions of GLRaV-3 and the respective methyltransferase and helicase sequences of other closteroviruses, such as Beet yellows virus, Citrus tristeza virus, and lettuce infectious yellow virus. Consequently, the DNA molecules coding for GLRaV-3 methyltransferase or helicase can also be used to produce transgenic cultivars other than grape, such as lettuce, beets, citrus and the like, which are resistant to closteroviruses other than grapevine leafroll, such as tristeza virus. These include cultivars of lemon, lime, orange, grapefruit, pineapple, tangerine, and the like, such as Joppa, Maltaise Ovale, Parson (Parson Brown), Pera, Pineapple, Queen, Shamouti, Valencia, Tenerife, Imperial Doblefina, Washington Sanguine, Moro, Sanguinello Moscato, Spanish Sanguinelli, Tarocco, Atwood, Australian, Bahia, Baiana, Cram, Dalmau, Eddy, Fisher, Frost Washington, Gillette, LengNavelina, Washington, Satsuma Mandarin, Dancy, Robinson, Ponkan, Duncan, Marsh, Pink Marsh, Ruby Red, Red Seedless, Smooth Seville, Orlando Tangelo, Eureka, Lisbon, Meyer Lemon, Rough Lemon, Sour Orange, Persian Lime, West Indian Lime, Bears, Sweet Lime, Troyer Citrange, and Citrus trifoliata.

Plant tissue suitable for transformation include leaf tissue, root tissue, meristems, zygotic and somatic embryos, anthers, and the like. It is particularly preferred to utilize embryos obtained from anther cultures. All of these tissues can be transformed using techniques well known to the skilled artisan. For additional information, WO 97/22700 is incorporated herein by reference.

The expression system of the present invention can be used to transform virtually any plant tissue under suitable conditions. Tissue cells transformed in accordance with the present invention can be grown *in vitro* in a suitable medium to

impart grapevine leafroll virus resistance, as well as beet yellows virus resistance, *Citrus tristeza* virus resistance, and lettuce infectious yellows virus resistance.

Transformed cells can be regenerated into whole plants such that the protein or polypeptide imparts resistance to grapevine leafroll virus in the intact transgenic
5 plants. In either case, the plant cells transformed with the recombinant DNA expression system of the present invention are grown and caused to express a DNA molecule corresponding to those taught herein, thus, imparting viral resistance.

One technique of transforming plants with the DNA molecules in accordance with the present invention is by contacting the tissue of such plants with an inoculum
10 of a bacteria transformed with a vector comprising a gene in accordance with the present invention which imparts grapevine leafroll resistance. Generally, this procedure involves inoculating the plant tissue with a suspension of bacteria and incubating the tissue for 48 to 72 hours on regeneration medium without antibiotics at 25-28 C.

15 Bacteria from the genus *Agrobacterium* can be utilized to transform plant cells. Suitable species of such bacterium include *Agrobacterium tumefaciens* and *Agrobacterium rhizogenes*. *Agrobacterium tumefaciens* (e.g., strains C58, LBA4404, or EHA105) is particularly useful due to its well-known ability to transform plants.

Another approach to transforming plant cells with a gene which imparts
20 resistance to pathogens is particle bombardment (also known as biolistic transformation) of the host cell. This can be accomplished in one of several ways, such as those disclosed in U.S. Patent Nos. 4,945,050, 5,036,006, and 5,100,792, all to Sanford et al., and in Emerschad et al., Plant Cell Reports, 14:6-12 (1995), which are hereby incorporated by reference. When inert particles are utilized, the vector can
25 be introduced into the cell by coating the particles with the vector containing the heterologous DNA. Alternatively, the target cell can be surrounded by the vector so that the vector is carried into the cell by the wake of the particle. Biologically active particles (e.g., dried bacterial cells containing the vector and heterologous DNA) can also be propelled into plant cells.

30 Once grape plant tissue is transformed in accordance with the present invention, it is regenerated to form a transgenic grape plant. Generally, regeneration

is accomplished by culturing transformed tissue on medium containing the appropriate growth regulators and nutrients to allow for the initiation of shoot meristems. Appropriate antibiotics are added to the regeneration medium to inhibit the growth of *Agrobacterium* and to select for the development of transformed cells.

5 Following shoot initiation, shoots are allowed to develop tissue culture and are screened for marker gene activity.

The DNA molecules of the present invention can be made capable of transcription to a messenger RNA, which, although encoding for a GLRaV-3 protein or polypeptide, does not translate to the protein. This is known as RNA-mediated
10 resistance. When a *Vitis* scion or rootstock cultivar is transformed with such a DNA molecule, the DNA molecule can be transcribed under conditions effective to maintain the messenger RNA in the plant cell at low level density readings. Density readings of between 15 and 50, using a Hewlet ScanJet and Image Analysis Program having default settings, are preferred.

15 The grapevine leafroll virus proteins or polypeptides can also be used to raise antibodies or binding portions thereof or probes. The antibodies can be monoclonal or polyclonal. A description of the theoretical basis and practical methodology of fusing such cells is set forth in Kohler and Milstein, Nature, 256:495 (1975), and Milstein and Kohler, Eur. J. Immunol., 6:511 (1976), hereby incorporated by reference.
20 Procedures for raising polyclonal antibodies are also well known to the skilled artisan. This and other procedures for raising polyclonal antibodies are disclosed in Harlow et. al., editors, Antibodies: A Laboratory Manual (1988), which is hereby incorporated by reference.

In addition to utilizing whole antibodies, binding portions of such antibodies
25 can be used. Such binding portions include Fab fragments, F(ab')₂ fragments, and Fv fragments. These antibody fragments can be made by conventional procedures, such as proteolytic fragmentation procedures, as described in Goding, Monoclonal Antibodies: Principles and Practice, New York: Academic Press, pp. 98-118 (1983), hereby incorporated by reference.

30 The present invention also relates to probes found either in nature or prepared synthetically by recombinant DNA procedures or other biological procedures.

Suitable probes are molecules which bind to grapevine leafroll viral antigens identified by the monoclonal antibodies of the present invention. Such probes can be, for example, proteins, peptides, lectins, or nucleic acid probes.

The antibodies or binding portions thereof or probes can be administered to grapevine leafroll virus infected scion cultivars or rootstock cultivars. Alternatively, at least the binding portions of these antibodies can be sequenced, and the encoding DNA synthesized. The encoding DNA molecule can be used to transform plants together with a promoter which causes expression of the encoded antibody when the plant is infected by grapevine leafroll virus. In either case, the antibody or binding portion thereof or probe will bind to the virus and help prevent the usual viral response.

Antibodies raised against the GLRaV-3 proteins or polypeptides of the present invention or binding portions of these antibodies can be utilized in a method for detection of grapevine leafroll virus in a sample of tissue, such as tissue from a grape scion or rootstock. Antibodies or binding portions thereof suitable for use in the detection method include those raised against a proteinase, a methyltransferase, a helicase, and a protein having a sequence according to SEQ ID NO: 13 in accordance with the present invention. Any reaction of the sample with the antibody is detected using an assay system which indicates the presence of grapevine leafroll virus in the sample. A variety of assay systems can be employed, such as enzyme-linked immunosorbent assays, radioimmunoassays, gel diffusion precipitin reaction assays, immunodiffusion assays, agglutination assays, fluorescent immunoassays, protein A immunoassays, or immunoelectrophoresis assays.

The DNA sequences of the present invention can also be used to clone additional fragments having similar sequences. By "similar sequences" is meant a protein or nucleic acid molecule exhibiting 70%, preferably 80%, and most preferably 90% identity to a reference amino acid sequence or nucleic acid sequence. For proteins, the length of comparison sequences will generally be at least 15 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably 35 amino acids or greater. For nucleic acids, the length of comparison sequences will generally be at least 50 nucleotides, preferably at least 60 nucleotides,

more preferably at least 75 nucleotides, and most preferably 110 nucleotides or greater.

Sequence identity, at the amino acid levels, is typically measured using sequence analysis software (for example, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705, BLAST, or PILEUP/PRETTYBOX programs). Such software matches identical or similar sequences by assigning degrees of homology to various substitutions, deletions, and/or other modifications.

The present invention also includes nucleic acids that selectively hybridize to GLRaV-3 sequences of the present invention. Hybridization may involve Southern analysis (Southern Blotting), a method by which the presence of DNA sequences in a target nucleic acid mixture are identified by hybridization to a labeled oligonucleotide or DNA fragment probe. Southern analysis typically involves electrophoretic separation of DNA digests on agarose gels, denaturation of the DNA after electrophoretic separation, and transfer of the DNA to nitrocellulose, nylon, or another suitable membrane support for analysis with a radiolabeled, biotinylated, or enzyme-labeled probe as described in Sambrook et al., (1989) Molecular Cloning, 2nd edition, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Hybridization often includes the use of a probe. It is generally preferred that a probe of at least 20 nucleotides in length be used, preferably at least 50 nucleotides, more preferably at least about 100 nucleotides.

A nucleic acid can hybridize under moderate stringency conditions or high stringency conditions to a nucleic acid disclosed herein. High stringency conditions are used to identify nucleic acids that have a high degree of homology or sequence identity to the probe. High stringency conditions can include the use of a denaturing agent such as formamide during hybridization, e.g., 50% formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM NaCl, and 75 mM sodium citrate at 42°C. Another example is the use of 50% formamide, 5X SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5x Denharts solution, sonicated salmon sperm DNA (50 ug/mL) 0.1% SDS, and 10%

dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC and 0.1% SDS.

Alternatively, low ionic strength washes and high temperature can be employed for washing.

Moderate stringency conditions are hybridization conditions used to identify
5 nucleic acids that have less homology or identity to the probe than do nucleic acids
under high stringency. All of these techniques are well known to the artisan skilled in
molecular biology.

The following examples are provided to illustrate embodiments of the present
invention and are by no means intended to limit its scope.

10

Examples

The examples cited herein incorporate by reference Examples 1-12, and
Examples 14-18 in their entirety from WO 97/22700, published 26 June, 1997, which
is based on U.S. Application 60/009,008 filed 21 December 1995.

15

Example 1: Nucleotide Sequence and Open Reading Frames

Cloning and sequencing of the GLRaV-3 genomic DNA was performed
exactly as described in WO 97/22700, published 26 June 1997 except as follows.

The genome of GLRaV-3 was determined after the additional 4,765
20 nucleotides on the 5' terminal portion were obtained and sequenced. The complete
genome of GLRaV-3 contains 17,919 nucleotides and contained 13 ORFs with a 5'
untranslated region of 158 nucleotides and a 3' untranslated region of 276 nucleotides
(Figure 1). The ORF1a, containing 6,714 nucleotides, encoded a large polyprotein
with a *Mr* of 245,277. With a +1 frameshift mechanism, it is also possible to produce
25 a large fusion protein (from ORF 1a and ORF 1b) of *Mr* of 305,955. Surprisingly,
GLRAV-3 did not contain a papain-like cysteine proteinase; instead, a proteinase
domain similar to the hepatitis C virus (Hijikata et al., Proc. Natl. Acad. Sci. USA
90:10773-10777 (1993), which is hereby incorporated by reference) was identified.
The metyltransferase domain and the helicase domain were similar to those of other
30 closteroviruses.

Based upon the original partial sequencing of the helicase, database searching indicated that the C-terminal portion of this protein shared significant similarity with the Superfamily 1 helicase of positive-strand RNA viruses. Comparison of the conserved domain region (291 amino acids) showed a 38.4% identity with an additional 19.7% similarity between GLRaV-3 and BYV and a 32.4% identity with an additional 21.1% similarity between GLRaV-3 and LIYV. Six helicase conserved motifs of Superfamily 1 helicase of positive-strand RNA viruses (Hodgman, Nature, 333:22-23 (Erratum 578) (1988) and Koonin et al., Critical Reviews in Biochemistry and Molecular Biology, 28:375-430 (1993), hereby incorporated by reference) were also retained in GLRaV-3. Analysis of the phylogenetic relationship in helicase domains between GLRaV-3 and the other positive-strand RNA viruses placed GLRaV-3 along with the other closteroviruses, including BYV, CTV, and LIYV, into the "tobamo" branch of the alphavirus-like supergroup. Nucleotide ("nt") and amino acid ("aa") sequence similarity was calculated from perfect matches after aligning with the GCG program GAP; the percentages in parentheses are the percentages calculated by the GAP program, which employs a matching table based on evolutionary conservation of amino acids (Devereux et al., Nucleic Acids Res., 12:387-395 (1984), hereby incorporated by reference). The sources for the BYV, CTV, and LIYV sequences were, respectively, Agranovsky et al., Virology 198:311-324 (1994), Karasev et al., Virology 208: 511- (1995), and Klaassen et al, Virology 208:99-110 (1995) and Rappe et al., Virology 199:35-41 (1994), hereby incorporated by reference.

ORF 1b started at nucleotide 6877 of SEQ ID NO: 1 and went to nucleotide 8475 as given in SEQ ID NO: 10 (Figure 12). This portion encoded for a protein having the amino acid sequence listed in SEQ ID NO: 11 (Figure 13). Database screening of this protein revealed a significant similarity to the Supergroup 3 RdRp of the positive-strand RNA viruses. Sequence comparison of GLRaV-3 with BYV, LIYV, and CTV over a 313-amino acid sequence fragment revealed a striking amino acid sequence similarity among eight conserved motifs. The best alignment was with BYV, with 41.2% identity and 19.8% additional similarity while the least alignment was with LIYV, with 35.9% identity and 20.5% additional similarity. Analysis of

phylogenetic relationships of the RdRp domains of the alphavirus-like supergroup viruses again placed GLRaV-3 into a “tobamo” branch along with other closteroviruses, BYV, CTV, BYSV, and LIYV.

ORF 2 through ORF 10 were exactly as described in Example 13 of WO 97/22700, published 26 June 1997.

ORF 11 encoded an unidentified polypeptide having a calculated *Mr* of 3,933.

ORF 12 was exactly as described for ORF 11 in Example 13 of WO 97/22700, published 26 June 1997. After ORF 12, a 3' untranslated region was obtained having the sequence listed in SEQ ID NO: 14.

Other Embodiments

All publications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication was specifically and individually indicated to be incorporated by reference.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is intended to cover any variations, uses, or adaptations following, in general, the principles of the invention and including such departures from the present disclosure within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the appended claims.

What is Claimed:

1. An isolated grapevine leafroll virus protein or polypeptide selected from the group of a polyprotein comprising a proteinase or a methyltransferase; a proteinase; a methyltransferase; a helicase having an amino terminal amino acid sequence of ValGlyGluSer; a protein consisting of the amino acid sequence of SEQ ID NO: 11; and a protein consisting of the amino acid sequence of SEQ ID NO: 13.
2. The isolated protein or polypeptide of claim 1, wherein the protein or polypeptide is a polyprotein having a molecular weight of from 242 to 248 kDa.
3. The isolated protein or polypeptide of claim 2, wherein the polyprotein comprises the amino acid sequence of SEQ ID NO: 15.
4. The isolated protein or polypeptide of claim 1, wherein the proteinase comprises the amino acid sequence of SEQ ID NO: 5.
5. The isolated protein or polypeptide of claim 1, wherein the methyltransferase comprises the amino acid sequence of SEQ ID NO: 7.
6. An isolated RNA molecule encoding a protein or polypeptide of claim 1.
7. An isolated DNA molecule having a nucleotide sequence of SEQ ID NO: 2 or SEQ ID NO: 14, or encoding a protein or polypeptide of claim 1.
8. The isolated DNA molecule of claim 7, wherein the protein or polypeptide is a polyprotein having a molecular weight of from 242 to 248 kDa.
9. The isolated DNA molecule of claim 8, wherein the polyprotein comprises the amino acid sequence of SEQ ID NO: 15.

10. The isolated DNA molecule of claim 9, wherein the DNA molecule comprises the nucleotide sequence of SEQ ID NO: 3.

5 11. The isolated DNA molecule of claim 7, wherein the protein or polypeptide is a proteinase comprising the amino acid sequence of SEQ ID NO: 5.

12. The isolated DNA molecule of claim 11, wherein the DNA molecule comprises the nucleotide sequence of SEQ ID NO: 4.

10

13. The isolated DNA molecule of claim 7, wherein the protein or polypeptide is a methyltransferase comprising the amino acid sequence of SEQ ID NO: 7.

15

14. The isolated DNA molecule of claim 13, wherein the DNA molecule comprises the nucleotide sequence of SEQ ID NO: 6.

15. The isolated DNA molecule of claim 7, wherein the protein or polypeptide is a helicase comprising the amino acid sequence of SEQ ID NO: 9.

20

16. The isolated DNA molecule of claim 15, wherein the DNA molecule comprises the nucleotide sequence of SEQ ID NO: 8.

17. The isolated DNA molecule of claim 7, wherein the DNA molecule comprises the nucleotide sequence of SEQ ID NO: 10.

25

18. The isolated DNA molecule of claim 7, wherein the DNA molecule comprises the nucleotide sequence of SEQ ID NO: 12.

30 19. An expression system comprising an expression vector into which is inserted a heterologous DNA molecule of claim 7.

20. The expression system of claim 19, wherein the heterologous DNA molecule is inserted in sense orientation.

5 21. The expression system of claim 19, wherein the heterologous DNA molecule is inserted in antisense orientation.

22. A host cell transformed with a heterologous DNA molecule of claim 7.

10 23. The host cell of claim 22, wherein the host cell is selected from the group of *Agrobacterium vitis* and *Agrobacterium tumefaciens*.

24. The host cell of claim 22, wherein the host cell is a grape cell or a citrus cell.

15 25. A transgenic plant or transgenic plant component comprising the DNA molecule according to claim 7.

20 26. The transgenic plant or transgenic plant component of claim 25, wherein said transgenic plant component is a scion.

27. The transgenic plant or transgenic plant component of claim 25, wherein said transgenic plant component is a rootstock.

25 28. The transgenic plant or transgenic plant component of claim 25, wherein said transgenic plant component is a somatic embryo.

29. A method of conferring viral disease resistance to a plant or plant component, said method comprising the steps of :

(a) transforming a plant cell with a DNA molecule according to claim 7 which is expressed in said plant or plant component; and

5 (b) regenerating a transgenic plant or transgenic plant component from said plant cell.

30. The method of claim 29, wherein said plant or plant component is resistant to a grapevine leafroll virus selected from the group of GLRaV-1, GLRaV-2,
10 GLRaV-3, GLRaV-4, GLRaV-5, and GLRaV-6.

31. The method of claim 29, wherein said plant or plant component is resistant to a beet yellows virus, lettuce infectious yellows virus, or citrus tristeza virus.

15 32. An antibody or binding portion thereof or probe recognizing the protein or polypeptide according to claim 1.

33. A method for detecting a virus in a sample, said method comprising:

20 (a) contacting a sample with the antibody of claim 32 under conditions that allow for complex formation between said antibody and said virus; and

(b) detecting said complexes as an indication that said virus is present in said sample.

25 34. A method for detecting a viral nucleic acid molecule in a sample, said method comprising:

(a) contacting a sample with the DNA of claim 7 or a fragment thereof under conditions that allow for complex formation between said DNA and said virus; and

30 (b) detecting said complexes as an indication that said virus is present in said sample.

The present invention relates to an isolated GLRaV-3 protein or polypeptide selected from a group of a polyprotein, a proteinase, a methyltransferase, a helicase, and an RNA-dependent RNA polymerase. The encoding DNA molecule either alone
5 in isolated form or in an expression system, a host cell, or a transgenic grape plant is also disclosed. Another aspect of the present invention relates to a method of imparting grapevine leafroll resistance to grape plants by transforming them with the DNA molecule of the present invention.

Figure 1

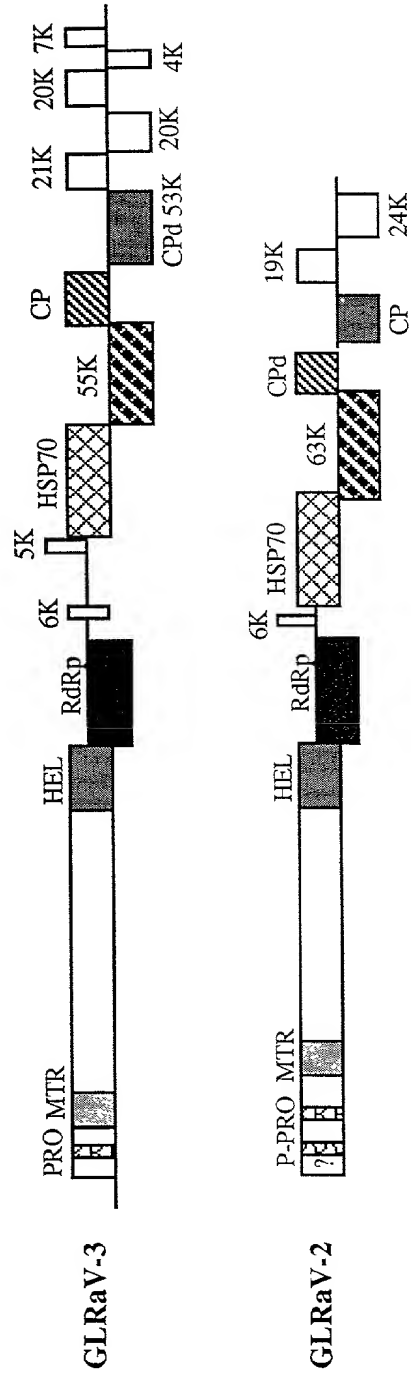


Figure 2

ctaagtaaca cctaggaatt tctacctaag attcaacttc tttctttttc tagtttttaa 60
ttttcctgct gtttgaggga agtttgccct tcttcttcog tcttccttcg taaaccatta 120
tttctatttc ctctcctttt aagtttttaa gtttcgctat ggactacatt cgcccattgc 180
gcgtttttct ctttcctcac gttaataaca ccttgagta cgttaggtac aacaaggcca 240
atgggtgatgt aggagctttc ctaaccacca tgaagttcat agggaaactg aagttgtcgg 300
acttcacacc caggtgcgca gctatgattt acattggaaa gtcaccaaa ggggtgaagc 360
gtacgtttgt cccccacca gttaaagggt ttgcacggca gtacgctgtt gtcagcggct 420
cagtcagcgc gctgagaggg gatggttaaga aggtcttgat ggaggcaagg acctcaactt 480
ccgcaacttc cgacgtgtct gatttcgacg tctgattcga agctgtttct aatgcattac 540
ttgtcgtaca ctaccaccgg gtagtgccgt atgccccgt caagcgcgag cagcctaaac 600
cggctgttaa gcaagatgag cagaagccca aacggcaagc gtcacattgg gctgttaagc 660
caacagctgt tggcgtccac gtaccacttc ctaaaaaaca ggaagcactg gagccagcgc 720
aatcagtccc acaacagctc ttggaggaga aggcgcgctt gacgtttggc cttttcttca 780
gtaaagggtg ggggtgatgag agcgacgctg tcatcttgcg gaaagggaaa ttgtttaaca 840
gggcccttaa tgttcctatt gatgtaaaga acacgttcgt ttgggctaaa atctgggatg 900
aagcctctcg taggagaggg tatttttacg tcaagatag agctgttaaa ttcttcccta 960
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tctcatcttc cttttcgata ggtttcttga tgcaccttg ctttagatcg ttaaagggtca 1200
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cattcgctaa tgccatgcgg agctgtttca atggaatctt ttccaggagg tgtggtaatg 1680

Figure 2-cont.

tgtgcttctt cgatattggg gggagcttca cgtatcatgt caaagctggc catgtgaact 1740
 gtcatgtatg caatccagtc ctagacgtta aagatgtgaa gcgagagaatc aatgagatcc 1800
 tctttctttc cacagctggg ggagattcgt acgtgtccag tgaccttcta actgaagcgg 1860
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 agaaggggtgc gctggttttc gacatagctc ttatgttccc cgtggagttg ttgtacggta 2040
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Figure 2-cont.

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Figure 2-cont.

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Figure 2-cont.

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Figure 2-cont.

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Figure 2-cont.

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Figure 2-cont.

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Figure 2-cont.

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Figure 2-cont.

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Figure 2-cont.

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Figure 3

```
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tttctatttc ctctcctttt aagtttttaa gtttcgct 158
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Figure 4

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Figure 4-cont.

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Figure 4-cont.

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Figure 4-cont.

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Figure 5

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Figure 6

VSGSVSALRG	DGKKVLMEAR	TSTSATSDVS	DFDVVFEAVS	NALLVVHYHR	50
VVPYAPVKRE	QPKPAVKQDE	QKPKRQASHW	AVKPTAVGVH	VPLPKKQEAL	100
EPAQSVPQQS	LEEKAALTFG				120

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Figure 7

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Figure 8

LKPREREKLR	ELFPELSIQF	SDSVRSSHPF	ANAMRSCFNG	IFSRRCGNVC	FFDIGGSFTY	60
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QNCDSRADAG	FMVDVYDISP	QQVAEAMDKK	GALVFDIALM	FPVELLYGNG	EVYLEELDTL	180
VKREGDYLAY	NVGQCGEMYE	HSFSNVSGFF	TFSYVRTSSG	NVFKLEYEGY	RCGYHHLTMC	240
RAQKSPGTEV	TYRSLVPSFV	GKSLVFIPVV	AG			272

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Figure 9

	MT I	MT Ia	MT II
Consensus #1P.....F.....S.H.....R...N.....D.GG.....H.C.P...D..D..R.....		
GLRaV2-MTR	MSEATQNSLTFYPQPELKFSSHSDHPAAAASRLLENETLVRLOGNS-VSDIGGCPLPHLHKTQRRVHVCRPVLGKDAQRRVVRDLQY		
BYV-MTR	MGEAVQSLTRAYPOFNLSFTHSVSDHPAAAGSRLLENETLASAKSS-FSDIGGCPLPHIK-RGSTDVHVCRPIYDMKDAQRRVSRELQA		
LIYV-MTR	LSMDEKMITNLFPDIQMSFNQKSYNGHGVFNAMRACENFYFSRKFKNSDYIDAGGDVSTLRSK-NHNVHICSPRLDLKDAARHIQRAVTI		
CTV-MTR	MSENQQVMLTRAYPEFNINFTSHSDHPVAAGSRALENHLVRKHAGTD-YSDVGCPLPHLRA-CHSGVHVCRPVYDKDAHRRVVRHQL		
LCV-MTR	LSTROKKIIVCDLFPHLKPEFKETQSSHPVNVVTVSNFVLYKMOEGRHFVDFGNIGTVINSE-CDDVHICNPVADSDRAKRRHVDNGLFL		
GLRaV3-MTR	LKPREREKLRLELFPPELSIQFSDSVRSHPFANAMRSCFNGIFSRRCGNVCFDIGGSFTYHVKAG-HVNCHVCNPVLGVKDVKRRINEILFL		
Consensus #1C.....C.....C.....V.VYD.....AM.....P.....		
GLRaV2-MTR	SNVRLG-DDD--KILEGPRN-IDICHYPLGACDHESSAMMWQVYDASLYEICGAMIKKSRITYLTMVTPGEFLDGRECVMESLDCELEV		
BYV-MTR	RGLVENLSRE--QLVEAQAR-VSVCPHLTGNCNVKSDVLIWQVYDASLINEIA SAMVLKESKVAYLTMVTPGELDEREAFALDALGCDVWV		
LIYV-MTR	DGLKG-----YGETI SPTCNKTEDCAVNRDIIIAVEYVDMTRDMA KAMLSHGRKPEFSCIIPPELFTKCNVELYEGRLKV--		
CTV-MTR	SKVSLDQSDGVKQVGMTVNT-NSVCGNIIIGECYHASEAMWQVYDVPLRELGRAMINKTSVCYMTMVTGPELDDARESFFIKDLDCSVEL		
LCV-MTR	AKSVG-----VSNNISVCNKLQAHCNHKSDRAVMVEYVDMTITMCQAMLAHGTIRLDF ILLLPGLLEDFTNITITFDGGCKI--		
GLRaV3-MTR	STAGGDSYVSSDLLTEAASKSVSYCSRESQNCDSRADAGFWVDVYDISPQQVAEAMDKKALVFDIALMFPVELLYGNGEVYLBELDTLV--		
Consensus #1D....Y.....H.....G..F.....		
GLRaV2-MTR	DVHADVMYKFGSSC--YSHKLSIIKDIMTTPYLTG-GFLFSVEMYEVRMGVNYFKITKSEVSPSISCTKLLRYRRANSDVVKVKLPRFD		
BYV-MTR	DTRRDMVOYKFGSSC--YCHKLSNIKSIIMLTPTAFTS-GNLFVSEMYENRMGVNYKITSAYSPEIRGVKTLRYRRACTEVVQVKLPRFD		
LIYV-MTR	TRIGDNVEYYGSGNETFSHSCQTLKDLISQVQFQG-GRVFKKTLHSGQLHFFSICICEKIEPGSVKLTYYQSRSELDKVTLRI PVKD		
CTV-MTR	DTADRNVVYCFNNSA--YTHYTSITCECMRTPCLVVD-GFLFTIEMVSLRCSVNYVCITKSSVCPRISETKRLRYRRCDSDLRIKIPRYS		
LCV-MTR	TKDDDKVYYYGDAAEAYTHDLNLRNIMTDLNLCVD-GTAFKKTLETSGYGFPRHPSLTLETFFPSGKIEFLTMVDKCKEKNMLVKVPMRN		
GLRaV3-MTR	KREGDYLAINVVGQCGEMYEHFSFNVSGFFTSVVRTSSGNVFKLEYEGYRCGYHHLTMCRQAQKSPGTEVTYRSLVPSFVGKSLVFI PVVAG		

Figure 10

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Figure 11

VGESFKSFY	KCYNAPPGG	KTTTLVDEFV	KSPNSTATIT	ANVGSSSEDIN	MAVKKRDPNL	60
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KPVVRSLSKR	PIGTDDVAE	INADVLCMT	QLEKSDMKRS	LKGKGKETPV	MTVHEAQGKT	240
FSDVVLFRTK	KADDSLFTKQ	PHILVGLSRH	TRSLVYAALS	SKLDDKVGTY	I	291

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Figure 13

MNFGPTFEGE	LVRKIPTSHF	VAVNGFLEDL	LDGCPAFDYD	FFEDDFETSD	QSFLIEDVRI	60
SESFHFTSK	IEDRFYSFIR	SSVGLPKRNT	LKCNLVTFEN	RNFNADRGCN	VGCDSDVAHE	120
LKEIFFEEVV	NKARLAEVTE	SHLSSNTMLL	SDWLDKRAPN	AYKSLKRALG	SFVFHPSMLT	180
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YHGMDTAEIA	AALRNNLGDI	RQYYTYELDI	SKYDKSQSAL	MKQVEELILL	TLGVDREVLS	300
TFFCGEYDSV	VRTMTKELVL	SVGSQRRSGG	ANTWLGNSLV	LCTLLSVVLR	GLDYSYIVVS	360
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KFGASKTSDI	DLLHEIFQSF	VDLSKGFNRE	DVIQELAKLV	TRKYKHSGWT	YSALCVLHVL	480
SANFSQFCRL	YYHNSVNLDV	RPIQRTELS	LLALKARILR	WKASRFAFSI	KRG	533

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Figure 14

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Figure 15

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Figure 16

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Figure 17

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66240-3060660

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Serial No.	:	To Be Assigned)	
)	Art Unit:
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)	
For	:	GRAPEVINE LEAFROLL VIRUS)	
		PROTEINS AND THEIR USES)	
)	

STATEMENT IN ACCORDANCE WITH 37 C.F.R. § 1.821(f)

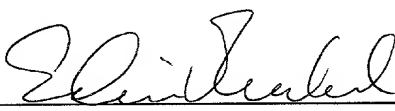
Assistant Commissioner for Patents
Washington, D.C. 20231
Box: Patent Application

Sir:

In accordance with 37 C.F.R. § 1.821(f), this statement confirms that the contents of the Sequence Listing (27 pages) of the subject application and on the computer readable 3.5" Diskette submitted herewith are the same.

Respectfully submitted,

Dated: April 29, 1999


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Registration No. 40,087

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SEQUENCE LISTING

<110> Gonsalves, Dennis
Ling, Kai-Shu

<120> GRAPEVINE LEAFROLL VIRUS PROTEINS AND THEIR USES

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<210> 4

<211> 360

<212> DNA

<213> grapevine leafroll-associated virus 3

<400> 4

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<210> 5

<211> 120

<212> PRT

<213> grapevine leafroll-associated virus 3

<400> 5

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Val Ser Gly Ser Val Ser Ala Leu Arg Gly Asp Gly Lys Lys Val Leu
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Met Glu Ala Arg Thr Ser Thr Ser Ala Thr Ser Asp Val Ser Asp Phe
      20                      25                      30

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Asp Val Val Phe Glu Ala Val Ser Asn Ala Leu Leu Val Val His Tyr

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35 40 45

His Arg Val Val Pro Tyr Ala Pro Val Lys Arg Glu Gln Pro Lys Pro
50 55 60

Ala Val Lys Gln Asp Glu Gln Lys Pro Lys Arg Gln Ala Ser His Trp
65 70 75 80

Ala Val Lys Pro Thr Ala Val Gly Val His Val Pro Leu Pro Lys Lys
85 90 95

Gln Glu Ala Leu Glu Pro Ala Gln Ser Val Pro Gln Gln Ser Leu Glu
100 105 110

Glu Lys Ala Ala Leu Thr Phe Gly
115 120

<210> 6
<211> 816
<212> DNA
<213> grapevine leafroll-associated virus 3

<400> 6

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<210> 7
<211> 272
<212> PRT
<213> grapevine leafroll-associated virus 3

<400> 7

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 35 40 45
 Val Cys Phe Phe Asp Ile Gly Gly Ser Phe Thr Tyr His Val Lys Ala
 50 55 60
 Gly His Val Asn Cys His Val Cys Asn Pro Val Leu Asp Val Lys Asp
 65 70 75 80
 Val Lys Arg Arg Ile Asn Glu Ile Leu Phe Leu Ser Thr Ala Gly Gly
 85 90 95
 Asp Ser Tyr Val Ser Ser Asp Leu Leu Thr Glu Ala Ala Ser Lys Ser
 100 105 110
 Val Ser Tyr Cys Ser Arg Glu Ser Gln Asn Cys Asp Ser Arg Ala Asp
 115 120 125
 Ala Gly Phe Met Val Asp Val Tyr Asp Ile Ser Pro Gln Gln Val Ala
 130 135 140
 Glu Ala Met Asp Lys Lys Gly Ala Leu Val Phe Asp Ile Ala Leu Met
 145 150 155 160
 Phe Pro Val Glu Leu Leu Tyr Gly Asn Gly Glu Val Tyr Leu Glu Glu
 165 170 175
 Leu Asp Thr Leu Val Lys Arg Glu Gly Asp Tyr Leu Ala Tyr Asn Val
 180 185 190
 Gly Gln Cys Gly Glu Met Tyr Glu His Ser Phe Ser Asn Val Ser Gly
 195 200 205
 Phe Phe Thr Phe Ser Tyr Val Arg Thr Ser Ser Gly Asn Val Phe Lys
 210 215 220
 Leu Glu Tyr Glu Gly Tyr Arg Cys Gly Tyr His His Leu Thr Met Cys
 225 230 235 240
 Arg Ala Gln Lys Ser Pro Gly Thr Glu Val Thr Tyr Arg Ser Leu Val
 245 250 255
 Pro Ser Phe Val Gly Lys Ser Leu Val Phe Ile Pro Val Val Ala Gly
 260 265 270

<210> 8
 <211> 873
 <212> DNA
 <213> grapevine leafroll-associated virus 3

<400> 8
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<210> 9
 <211> 291
 <212> PRT
 <213> grapevine leafroll-associated virus 3

<400> 9
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 20 25 30
 Pro Asn Ser Thr Ala Thr Ile Thr Ala Asn Val Gly Ser Ser Glu Asp
 35 40 45
 Ile Asn Met Ala Val Lys Lys Arg Asp Pro Asn Leu Glu Gly Leu Asn
 50 55 60
 Ser Ala Thr Thr Val Asn Ser Arg Val Val Asn Phe Ile Val Arg Gly
 65 70 75 80
 Met Tyr Lys Arg Val Leu Val Asp Glu Val His Met Met His Gln Gly

	85		90		95										
Leu	Leu	Gln	Leu	Gly	Val	Phe	Ala	Thr	Gly	Ala	Ser	Glu	Gly	Leu	Phe
			100					105					110		
Phe	Gly	Asp	Ile	Asn	Gln	Ile	Pro	Phe	Ile	Asn	Arg	Glu	Lys	Val	Phe
		115					120					125			
Arg	Met	Asp	Cys	Ala	Val	Phe	Val	Pro	Lys	Lys	Glu	Ser	Val	Val	Tyr
	130					135					140				
Thr	Ser	Lys	Ser	Tyr	Arg	Cys	Pro	Leu	Asp	Val	Cys	Tyr	Leu	Leu	Ser
145					150					155					160
Ser	Met	Thr	Val	Arg	Gly	Thr	Glu	Lys	Cys	Tyr	Pro	Glu	Lys	Val	Val
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Ser	Gly	Lys	Asp	Lys	Pro	Val	Val	Arg	Ser	Leu	Ser	Lys	Arg	Pro	Ile
			180					185					190		
Gly	Thr	Thr	Asp	Asp	Val	Ala	Glu	Ile	Asn	Ala	Asp	Val	Tyr	Leu	Cys
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<210> 10
 <211> 1599
 <212> DNA
 <213> grapevine leafroll-associated virus 3
 <400> 10

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<210> 11

<211> 533

<212> PRT

<213> grapevine leafroll-associated virus 3

<400> 11

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			20					25					30		

Gly	Cys	Pro	Ala	Phe	Asp	Tyr	Asp	Phe	Phe	Glu	Asp	Asp	Phe	Glu	Thr
		35					40					45			

Ser	Asp	Gln	Ser	Phe	Leu	Ile	Glu	Asp	Val	Arg	Ile	Ser	Glu	Ser	Phe
	50					55					60				

Ser	His	Phe	Thr	Ser	Lys	Ile	Glu	Asp	Arg	Phe	Tyr	Ser	Phe	Ile	Arg
	65				70					75				80	

Asn Ser Leu Val Leu Cys Thr Leu Leu Ser Val Val Leu Arg Gly Leu
340 345 350

Asp Tyr Ser Tyr Ile Val Val Ser Gly Asp Asp Ser Leu Ile Phe Ser
355 360 365

Arg Gln Pro Leu Asp Ile Asp Thr Ser Val Leu Ser Asp Asn Phe Gly
370 375 380

Phe Asp Val Lys Ile Phe Asn Gln Ala Ala Pro Tyr Phe Cys Ser Lys
385 390 395 400

Phe Leu Val Gln Val Glu Asp Ser Leu Phe Phe Val Pro Asp Pro Leu
405 410 415

Lys Leu Phe Val Lys Phe Gly Ala Ser Lys Thr Ser Asp Ile Asp Leu
420 425 430

Leu His Glu Ile Phe Gln Ser Phe Val Asp Leu Ser Lys Gly Phe Asn
435 440 445

Arg Glu Asp Val Ile Gln Glu Leu Ala Lys Leu Val Thr Arg Lys Tyr
450 455 460

Lys His Ser Gly Trp Thr Tyr Ser Ala Leu Cys Val Leu His Val Leu
465 470 475 480

Ser Ala Asn Phe Ser Gln Phe Cys Arg Leu Tyr Tyr His Asn Ser Val
485 490 495

Asn Leu Asp Val Arg Pro Ile Gln Arg Thr Glu Ser Leu Ser Leu Leu
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Ala Leu Lys Ala Arg Ile Leu Arg Trp Lys Ala Ser Arg Phe Ala Phe
515 520 525

Ser Ile Lys Arg Gly
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<210> 12

<211> 111

<212> DNA

<213> grapevine leafroll-associated virus 3

<400> 12

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<210> 13

<211> 36

<212> PRT

<213> grapevine leafroll-associated virus 3

<400> 13

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Cys Arg Arg Arg
35

<210> 14

<211> 279

<212> DNA

<213> grapevine leafroll-associated virus 3

<400> 14

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<211> 2237

<212> PRT

<213> grapevine leafroll-associated virus 3

<400> 15

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20 25 30

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35 40 45

Phe Thr Pro Arg Cys Ala Ala Met Ile Tyr Ile Gly Lys Leu Thr Lys
50 55 60

Gly Val Lys Arg Thr Phe Val Pro Pro Pro Val Lys Gly Phe Ala Arg
 65 70 75 80
 Gln Tyr Ala Val Val Ser Gly Ser Val Ser Ala Leu Arg Gly Asp Gly
 85 90 95
 Lys Lys Val Leu Met Glu Ala Arg Thr Ser Thr Ser Ala Thr Ser Asp
 100 105 110
 Val Ser Asp Phe Asp Val Val Phe Glu Ala Val Ser Asn Ala Leu Leu
 115 120 125
 Val Val His Tyr His Arg Val Val Pro Tyr Ala Pro Val Lys Arg Glu
 130 135 140
 Gln Pro Lys Pro Ala Val Lys Gln Asp Glu Gln Lys Pro Lys Arg Gln
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 Ala Ser His Trp Ala Val Lys Pro Thr Ala Val Gly Val His Val Pro
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 Leu Pro Lys Lys Gln Glu Ala Leu Glu Pro Ala Gln Ser Val Pro Gln
 180 185 190
 Gln Ser Leu Glu Glu Lys Ala Ala Leu Thr Phe Gly Leu Phe Phe Ser
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 Lys Gly Gly Gly Asp Glu Ser Asp Ala Val Ile Leu Arg Lys Gly Lys
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 Leu Phe Asn Arg Ala Leu Asn Val Pro Ile Asp Val Lys Asn Thr Phe
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 Val Trp Ala Lys Ile Trp Asp Glu Ala Ser Arg Arg Arg Gly Tyr Phe
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 Tyr Val Lys Asp Arg Ala Val Lys Phe Phe Pro Ile Val Arg Gly Arg
 260 265 270
 Ala Thr Ile Glu Asp Phe Ile Val Asn Thr Ala Pro Gly Cys Asp Val
 275 280 285
 Ala Leu Pro Arg Ile Glu Leu Trp Ser Met Arg Glu Arg Ala Phe Val
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 Cys Thr Thr Lys Gly Trp Cys Trp Phe Asn Asn Glu Arg Leu Arg Gly
 305 310 315 320

Glu Ile Tyr Arg Arg Arg Cys Phe Ser Ser Ser Phe Ser Ile Gly Phe
 325 330 335
 Leu Met His Leu Gly Phe Arg Ser Leu Lys Val Ile Arg Phe Ala Gly
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 Thr Asn Ile Leu His Met Pro Ser Leu Asn Glu Glu Arg Thr Phe Gly
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 Trp Lys Gly Gly Asp Val Tyr Leu Pro Asn Val Pro Lys Thr Ala Ile
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 Val Ala Gly Asp Arg Thr Arg Leu Gly Gly Glu Ile Leu Ala Ser Val
 385 390 395 400
 Ala Asn Ala Leu Asn Gln Glu Glu Val Tyr Ser Ser Val Val Ser Ser
 405 410 415
 Ile Thr Asn Arg Leu Val Leu Arg Asp Gln Ser Ala Leu Leu Ser His
 420 425 430
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 Arg Glu Lys Pro Ser His Arg Cys Asp Val Phe Leu Lys Pro Arg Glu
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 Arg Glu Lys Leu Arg Glu Leu Phe Pro Glu Leu Ser Ile Gln Phe Ser
 465 470 475 480
 Asp Ser Val Arg Ser Ser His Pro Phe Ala Asn Ala Met Arg Ser Cys
 485 490 495
 Phe Asn Gly Ile Phe Ser Arg Arg Cys Gly Asn Val Cys Phe Phe Asp
 500 505 510
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 His Val Cys Asn Pro Val Leu Asp Val Lys Asp Val Lys Arg Arg Ile
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Arg Glu Ser Gln Asn Cys Asp Ser Arg Ala Asp Ala Gly Phe Met Val
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 Leu Tyr Gly Asn Gly Glu Val Tyr Leu Glu Glu Leu Asp Thr Leu Val
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 Lys Arg Glu Gly Asp Tyr Leu Ala Tyr Asn Val Gly Gln Cys Gly Glu
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 Met Tyr Glu His Ser Phe Ser Asn Val Ser Gly Phe Phe Thr Phe Ser
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 Tyr Val Arg Thr Ser Ser Gly Asn Val Phe Lys Leu Glu Tyr Glu Gly
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 Tyr Arg Cys Gly Tyr His His Leu Thr Met Cys Arg Ala Gln Lys Ser
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 705 710 715 720
 Lys Ser Leu Val Phe Ile Pro Val Val Ala Gly Ser Ser Val Ser Phe
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 Lys Thr Ile Val Leu Asp Ser Asp Phe Val Asp Arg Ile Tyr Ser Tyr
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 755 760 765
 Val Gly Ala Val Arg Ser Gln Lys Thr His Val Ile Thr Gly Ser Arg
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 Val Val His Ser Lys Val Asp Ile Ser Pro Asp Asp Met Trp Gly Leu
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Ser Val Tyr Ala Lys Ala Met Val His Asp Asn Phe Asn Val Leu Glu
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Thr Leu Met Ser Met Pro Arg Ala Phe Ile Arg Lys Val Pro Gly Ser
865 870 875 880
Val Val Val Thr Ile Cys Thr Ser Gly Ala Ser Asp Arg Leu Glu Leu
885 890 895
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Asn Ser Arg Leu Arg Val Phe Ser Arg Ala Ile Val Glu Asp Ser Ile
915 920 925
Lys Val Met Lys Ala Met Lys Thr Glu Asp Gly Lys Pro Leu Pro Ile
930 935 940
Thr Glu Asp Ser Val Tyr Ala Phe Ile Met Gly Asn Val Ser Asn Val
945 950 955 960
His Cys Thr Arg Ala Gly Leu Leu Gly Gly Ser Lys Ala Thr Val Val
965 970 975
Ser Ser Val Ser Lys Gly Leu Val Ala Arg Gly Ala Ala Thr Lys Ala
980 985 990
Phe Ser Gly Ile Thr Ser Phe Phe Ser Thr Gly Ser Leu Phe Tyr Asp
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Arg Gly Leu Thr Glu Asp Glu Arg Leu Asp Ala Leu Val Arg Thr Glu
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Leu Asn Asp Phe Thr Thr Phe Val Leu Arg Asn Lys Val Leu Ile Gly
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1075 1080 1085

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Lys Gly Leu Leu Pro Glu Ser Val Val Gly Glu Ala Pro Thr Gln Glu			
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Gly Asp Arg Glu Pro Val Gln Ser Ser Leu Val Ser Ser Pro Gln Ala			
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Lys Ser Pro Gly Val Pro Asn Gln Gln Pro Gln Ser Gln Gly Ala Thr
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Ala Leu Glu Pro Asp Tyr Thr Pro Met Thr Phe Glu Val Val Lys Thr
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Ser Leu Pro Gly Phe His Val Tyr Lys Ser Gly Thr Asp Leu Ile Phe
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Ile	Ala	Glu	Lys	Gly	Ile	Phe	Thr	Lys	Gly	Lys	Asp	Val	Asp	Ala	Val
		1875					1880					1885			
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1905					1910					1915					1920
Met	Val	Gly	Glu	Ser	Phe	Lys	Ser	Phe	Glu	Tyr	Lys	Cys	Tyr	Asn	Ala
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Pro	Pro	Gly	Gly	Gly	Lys	Thr	Thr	Thr	Leu	Val	Asp	Glu	Phe	Val	Lys
			1940					1945					1950		
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1985					1990					1995					2000
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Gly	Leu	Leu	Gln	Leu	Gly	Val	Phe	Ala	Thr	Gly	Ala	Ser	Glu	Gly	Leu
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Phe	Phe	Gly	Asp	Ile	Asn	Gln	Ile	Pro	Phe	Ile	Asn	Arg	Glu	Lys	Val
		2035					2040					2045			
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		2050				2055					2060				
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2065					2070					2075					2080
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				2085					2090					2095	
Val	Ser	Gly	Lys	Asp	Lys	Pro	Val	Val	Arg	Ser	Leu	Ser	Lys	Arg	Pro
			2100					2105					2110		

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 Lys Gly Lys Glu Thr Pro Val Met Thr Val His Glu Ala Gln Gly Lys
 2145 2150 2155 2160
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 2165 2170 2175
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 Arg Ser Leu Val Tyr Ala Ala Leu Ser Ser Lys Leu Asp Asp Lys Val
 2195 2200 2205
 Gly Thr Tyr Ile Ser Asp Ala Ser Pro Gln Ser Val Ser Asp Ala Leu
 2210 2215 2220
 Leu His Thr Phe Ala Pro Ala Gly Cys Phe Arg Gly Ile
 2225 2230 2235

COMBINED DECLARATION FOR PATENT
APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER
19603/2842 (CRF D-1676D)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

GRAPEVINE LEAFROLL VIRUS PROTEINS AND THEIR USES

the specification of which (check only one item below):

☒ is attached hereto.

☐ was filed as U.S. Patent Application Serial No. _____ on _____ and was amended on _____ (if applicable).

☐ was filed as PCT International Application Number _____ on _____ and was amended under PCT Article 19 on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specifications, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (IF PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
United States	60/083,404	April 29, 1998	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
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			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
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			<input type="checkbox"/> YES <input type="checkbox"/> NO

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Continued) (Includes Reference to PCT International Applications)				ATTORNEY'S DOCKET NUMBER 19603/2842 (CRF D-1676D)	
I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT International filing date of this application:					
PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:					
U.S. APPLICATIONS			STATUS (Check One)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED	
PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)			
POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. Michael L. Goldman, Registration No. 30,727, Gunnar G. Leinberg, Registration No. 35,584; Dennis M. Connolly, Registration No. 40,964; Edwin V. Merkel, Registration No. 40,087, Jeffery B. Arnold, Registration No. 39,540					
Send Correspondence to: Michael L. Goldman Nixon, Hargrave, Devans & Doyle LLP Clinton Square, P.O. Box 1051 Rochester, New York 14603			Direct telephone calls to: Michael L. Goldman (716) 263-1304		
201	FULL NAME OF INVENTOR	FAMILY NAME Gonsalves	FIRST GIVEN NAME Dennis	SECOND GIVEN NAME	
	RESIDENCE & CITIZENSHIP	CITY Geneva	STATE/FOREIGN COUNTRY New York	COUNTRY OF CITIZENSHIP United States	
	POST OFFICE ADDRESS	P.O. ADDRESS 595 Castle Street	CITY Geneva	STATE & ZIP CODE/COUNTRY New York 14456/USA	
202	FULL NAME OF INVENTOR	FAMILY NAME Ling	FIRST GIVEN NAME Kai-Shu	SECOND GIVEN NAME	
	RESIDENCE & CITIZENSHIP	CITY San Juan Bautista	STATE/FOREIGN COUNTRY California	COUNTRY OF CITIZENSHIP People's Republic of China	
	POST OFFICE ADDRESS	P.O. ADDRESS 2191 San Juan-Hollister Road, CA Highway 156	CITY San Juan Bautista	STATE & ZIP CODE/COUNTRY California 95045/USA	
203	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME	
	RESIDENCE & CITIZENSHIP	CITY	STATE/FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
	POST OFFICE ADDRESS	P.O. ADDRESS	CITY	STATE & ZIP CODE/COUNTRY	
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.					
SIGNATURE OF INVENTOR 201 UNSIGNED		SIGNATURE OF INVENTOR 202 UNSIGNED		SIGNATURE OF INVENTOR 203	
DATE		DATE		DATE	